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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,327	02/23/2001	William Osmond Charles Michael Cookson		5723

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EXAMINER	
SOUAYA, JEHANNE E	4

ART UNIT	PAPER NUMBER
1634	11

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,327	COOKSON ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 12-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in Paper No. 10.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino

acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Objections

2. Claims 3 and 5 are objected to because of the following informalities: the recitation of "the or each" is awkward. Suggested language is "the allele or each allele".

Claim Rejections - 35 USC § 112

Enablement

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The claims are broadly drawn to a method of diagnosing an individual as being asthmatic or having a predisposition to asthma wherein the method comprises demonstrating the presence or absence of one or more alleles associated with asthma, wherein the one or more alleles are situated at a locus in a region of chromosome 4 up to 1 megabase in length wherein the region contains the locus D4S3032 and/or D4S2921. The claims are further drawn to diagnosing asthma or a predisposition to asthma by detecting the presence of D4S3032*5 and/or D4S2921*13.

The claims encompass diagnosing an individual as being asthmatic or having a predisposition to asthma by demonstrating either the presence or absence of any allele associated with asthma wherein the allele is situated at a locus in a region of chromosome 4 up to 1 megabase in length wherein the region contains the locus the locus D4S3032 and/or D4S2921. Such claims cover a research project requiring extensive trial and error analysis, the results of which are unpredictable. The region encompassed by the claims is very large, containing a large number of possible genes and alleles that may or may not be associated with asthma, the identity of which the specification does not teach or describe. Such "alleles" encompass variants or mutants with loss of or altered functions of unknown, uncharacterized genes, whose association to asthma has not been demonstrated or described by the specification. The specification only teaches testing a single allele within this large region, and the results of such a study appear to be conflicting (detailed more fully below). The claims require analysis of a large region that can be up to a megabase on one side of the locus D4S3032 and/or D4S2921, containing unknown, uncharacterized genes and alleles.

The specification teaches that linkage disequilibrium occurs over 50-500 kb of DNA, however the claims do not require that the locus D4S3032 and/or D4S2921 be in the middle of the region that contains the unknown, uncharacterized allele. Further, the specification teaches that the recombination fraction between D4S3032 and D4S2921 is .5 to 1 megabase, therefore the claims actually encompass a region up to 3 megabases. Regardless of such, that is, even if the region covered only 1 megabase, or even 50-500 kilobases, the specification has not taught the identity of any asthma associated alleles within this large region. With regard to the likelihood that an asthma gene exists 500 kilobases on either side of the locus D4S3032 and/or D4S2921, the art teaches that linkage disequilibrium analysis can lead to false positives because of factors such as population stratification (March, R. Molecular Biotechnology, vol. 13, pp 113-122; see p. 116, col. 2). March teaches that because of such, linkage disequilibrium mapping is often used to fine-map a disease gene when a region of interest has already been mapped (for instance the cystic fibrosis gene). In the instant case, the specification does not teach of any specific genes or alleles associated with asthma in this large region, except for D4S3032*5 and D4S2921*13, however, it is unclear whether either of these alleles are diagnostic of asthma. It is further unclear how the results of the association analysis taught in the specification have associated any allele or gene in this large uncharacterized region with asthma. Further, the D4S3032*5 and D4S2921*13 alleles are drawn to a microsatellite repeat alleles, which March teaches (p. 118-119, bridging para) are less suitable for fine mapping or association analysis. March teaches that the large number of alleles becomes a problem when using haplotype based methods, are not usually intragenic, and may have relatively high variable mutation rates which may destroy linkage disequilibrium between a marker and disease mutation.

The specification teaches a study which tested the association between intermediate asthma associated phenotypes and the D4S3032*5 and D4S2921*13 alleles. The results taught in the specification are unclear and appear conflicting, however. For example, using the bronchial responsiveness to methacholine challenge test , the D4S3032*5 allele did not show a statistically significant association with panel C subjects, of which 44% were asthmatic. Therefore, the teachings of the specification appear to be conflicting as to a predictable association between the D4S3032*5 allele and asthma. Further, while the specification teaches a statistically significant association between the D4S2921*13 allele in panel A and panel C subjects using the eosinophilis test, the specification does not teach whether these results could be confirmed using other asthma associated tests. Eosinophilic infiltration, however, is not only associated with asthma, but with eosinophilic bronchitis (see Lee et al., Chest, vol. 120, pp 1114-1120, 2001). Lee teaches that in 21 patients determined to have eosinophilic infiltration, a methacholine challenge test was administered (see p. 1117, col. 1). Lee teaches that 5 of the 21 patients had positive results with the methacholine challenge test, indicating that they suffered from cough-variant asthma, while 16 of the patients with negative results for methacholine challenge received the diagnosis of eosinophilic bronchitis. As the specification does not teach whether statistically significant results were found with the D4S2921*13 allele and bronchial responsiveness to methacholine, for example, the skilled artisan would not be able to determine that the D4S2921*13 allele was predictably diagnostic of asthma.

The art is silent as to an association between D4S3032, or D4S2921, or any allele contained in a region up to 1 megabase on either side of and containing said loci, and asthma in

individuals. Given this lack of teaching, the art does not overcome the deficiencies in the specification.

Therefore, given the lack of a teaching of a predictable correlation between intermediate asthma phenotypes and D4S3032, or D4S2921, or any allele contained in a region up to 1 megabase containing the loci D4S3032, or D4S2921, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed. Firstly, the specification does not appear to have established a predictable correlation between the D4S3032*5 allele or the D4S2921*13 allele, and asthma. Further, the specification has not taught or described the identity of any other asthma associated alleles within the large region encompassed by the claims. The skilled artisan would be required to perform a large study with asthmatic patients and controls to establish whether any of the unknown, uncharacterized alleles in the large region encompassed by the claims was predictably diagnostic of asthma. Secondly, the claims broadly encompass diagnosing asthma or a predisposition to asthma based on either the presence or absence of any allele in a very large region that contains a large number of genes that have not been identified or characterized or associated with asthma. The claimed invention sets forth an invitation for further experimentation, however given the lack of guidance in the specification and the unpredictable and conflicting results set forth in the specification, such experimentation would be replete with trial and error analysis, which is considered undue.

Written Description

3. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass diagnosing an individual as being asthmatic or having a predisposition to asthma by demonstrating either the presence or absence of an allele associated with asthma wherein the allele is situated at a locus in a region of chromosome 4 up to 1 megabase in length wherein the region contains the locus D4S3032 and/or D4S2921. However, the specification has not taught or described any genes or alleles (other than D4S3032*5 or D4S2921*13) in this large region, let alone any associated with asthma. The specification only teaches testing two alleles within this large region, and the results of such are unclear (detailed more fully below) . The claims require analysis of a large region that can be up to a megabase on one side of the locus D4S3032, or D4S2921, containing unknown, uncharacterized genes and alleles, which have not been taught or described in the specification. Neither the specific structure, nor specific location of these alleles are taught or described in the specification, and the claimed invention only identifies this large number of possible alleles by their function (association to asthma). The specification does not describe this large number of unknown alleles such that the structure of such alleles would be apparent by their function. Further, with regard to claim 11, the identification of such alleles is carried out by sequences whose structures themselves are undefined. The specification does not define what is encompassed by "substantially similar", and therefore, the structure of these sequences cannot be envisioned. The specification teaches a study which tested the association between intermediate asthma associated phenotypes and the D4S3032*5 and D4S2921*13 alleles. The results taught in the specification are unclear and appear conflicting, however. For example, using the bronchial

responsiveness to methacholine challenge test , the D4S3032*5 allele did not show a statistically significant association with panel C subjects, of which 44% were asthmatic. Therefore, the teachings of the specification appear to be conflicting as to a predictable association between the D4S3032*5 allele and asthma. Further, while the specification teaches a statistically significant association between the D4S2921*13 allele in panel A and panel C subjects using the eosinophilis test, the specification does not teach whether these results could be confirmed using other asthma associated tests. Eosinophilic infiltration, however, is not only associated with asthma, but with eosinophilic bronchitis (see Lee et al., Chest, vol. 120, pp 1114-1120, 2001). Lee teaches that in 21 patients determined to have eosinophilic infiltration, a methacholine challenge test was administered (see p. 1117, col. 1). Lee teaches that 5 of the 21 patients had positive results with the methacholine challenge test, indicating that they suffered from cough-variant asthma, while 16 of the patients with negative results for methacholine challenge received the diagnosis of eosinophilic bronchitis. As the specification does not teach whether statistically significant results were found with the D4S2921*13 allele and bronchial responsiveness to methacholine, for example, the skilled artisan would not be able to determine that the D4S2921*13 allele was predictably diagnostic of asthma.

The disclosure of the alleles D4S3032*5 and D4S2921*13, whose association to asthma is unclear, are not representative of the extremely large number of possible alleles which could be located up to 1 megabase (or even 50-500 kilobases) of D4S3032 or D4S2921, which are associated with asthma. The specification does not demonstrate a correlation or association between any of these unknown, uncharacterized alleles and asthma. The structure or specific location of these alleles are not taught or described. Further, were an association between

D4S3032*5 or D4S2921*13 and asthma shown, these alleles would not be representative of the hundreds of uncharacterized, unknown alleles, that are be encompassed by the claimed method. There is no correlation between the structures of these alleles and an association to asthma such that the skilled artisan would be able to identify other asthma associated alleles in the large region encompassed by the claimed invention. The region encompassed by the claims contains a large number of possible genes and alleles that may or may not be associated with asthma, the identity of which the specification does not teach or describe. Such "alleles" encompass variants or mutants with loss of or altered functions of unknown, uncharacterized genes, whose association to asthma has not been demonstrated or described by the specification.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Based on the lack of teaching or description of a representative number of asthma associated alleles within the extremely large region of DNA recited in the claims, the skilled artisan cannot envision the detailed chemical structure of the encompassed alleles. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. It is noted that the instant claims are drawn to methods, however, the

methods require the identification of uncharacterized, unknown alleles that have not been taught or described in the specification.

Consequently, the specification fail to provide adequate written description of the invention of claims 1-11.

Indefinite

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite. The claim is drawn to diagnosing an individual as being asthmatic or as having a predisposition to asthma by demonstrating the absence of an allele which is associated with asthma. This recitation seems at opposite with the preamble as it is unclear how the absence of an asthma associated allele is predictive of asthma. Additionally, claim 1 recites the phrase "wherein the one or more alleles" twice. It is unclear if the second recitation is in error or if the first recitation was meant to signify an additional limitation that has been left out.

Claim11 is indefinite as it is unclear what is meant by "substantially similar sequences". The specification does not define this term and therefore the structure of the resulting nucleic acids is unclear. Further, it is unclear if the recitation of "identified" encompasses the exact sequence of SEQ ID NOS 1-4, or if the recitation encompasses sequences of variable complementarity to SEQ ID NOS 1-4.

Conclusion

6. No claims are allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634

Jehanne Souaya
3/20/03